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Heterocycle Annulation of Enolizable Vinyl Quinone Imides. Dihydroquinolines and Quinolines from Thermal 6π-Electrocyclizations and Indoles from Photochemical Cyclizations

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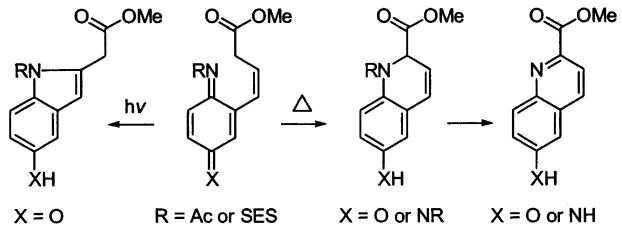
ABSTRACT



Enolizable vinyl quinone mono- and diimide substrates yield protected 6-hydroxy and 6-amino dihydroquinolines by thermal electrocyclization. Aromatization provides the corresponding quinolines in quantitative yields. The quinone monoimide substrates undergo clean photochemical conversion to 5-hydroxy indoles.

Quinoline-containing natural products have attracted the attention of synthetic and medicinal chemists for many decades. The parent bicyclic substructure is found in natural products that exhibit a wide spectrum of biological activities and the quinoline, di- and tetrahydroquinoline, and oxo-quinoline moieties are found in a large number of medicinally interesting compounds.[1,2]

Numerous synthetic methods have been developed for the preparation of this class of heterocycles.[1,3] Most of the classical preparations lead directly to aromatized quinolines or proceed through dihydroquinolines without the isolation of these sensitive intermediates. However, there is some interest in the preparation of stable dihydroquinoline derivatives.[3,4] We now wish to report a new synthetic approach that gives rise to protected 2-carboxy 6-amino and 6-hydroxy dihydroquinolines and the facile elaboration of these products to the corresponding 2-substituted quinolines. In addition, we wish to describe a variation of our sequence that efficiently gives rise to indoles.

Generalization of the electrocyclization-based annulation recently discovered in our laboratories[5] could provide access to a variety of heterocycles. In the previously established applications of this approach, enolization of vinyl quinones **1** followed by thermal 6π-electrocyclic ring closure of the resulting quinone methides **2** provided benzopyran products

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(1) See, e.g.: Jones, G. In *Chemistry of Heterocyclic Compounds* "*Quinolines*"; John Wiley & Sons: New York, 1977 (part 1), 1982 (part 2), 1990 (part 3); Vol. 32.

(2) Michael, J. P. *Nat. Prod. Rep.* **2001**, *17*, 603−620 and previous reviews in this series.

(3) (a) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761−785. (b) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269−3271.

(4) See, e.g.: Altamura, M.; Meini, S.; Quartara, L.; Maggi, C. A. *Regul. Pept.* **1999**, *80*, 13−26.

(5) Parker, K. A., Mindt, T. L. *Org. Lett.* **2001**, *24*, 3875−3878.

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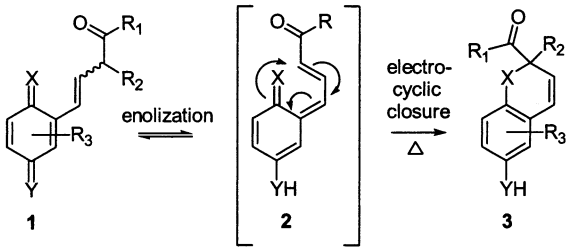
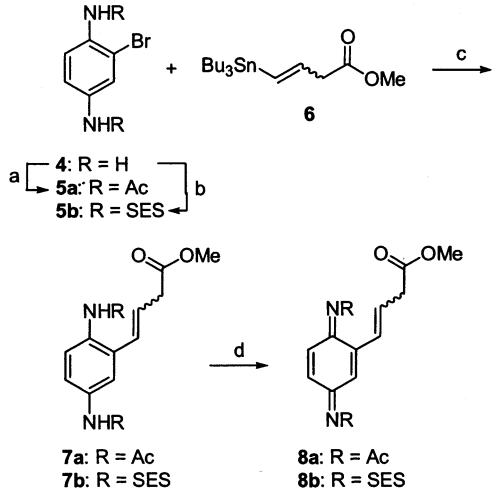
3 (Scheme 1; X, Y = O). Extension of this class of reactions to the preparation of nitrogen heterocycles would rely on the isomerization of enolizable vinyl quinone imides **1**[6] (Scheme 1; X, Y = NR or X = NR, Y = O).

Scheme 1. Generalization of Two-Step Heterocycle Annulation



The preparation of substrates for these investigations would be based on the Stille coupling of vinyl tin reagents with amide derivatives[7] of bromo phenylenediamines or of bromo amino phenols as shown in Schemes 2 and 4. The desired

Scheme 2. Preparation of Vinyl Quinone Diimide Substrates[a]



[a] (a) Ac_2O, py, rt (96%); (b) SESCl,[11] py, rt (64%); (c) $(Ph_3P)_4Pd$, toluene, reflux (50% **5a**, 58% **5b**); (d) $Pb(OAc)_4$, $CHCl_3$, rt (92% **8a**, 100% **8b**).

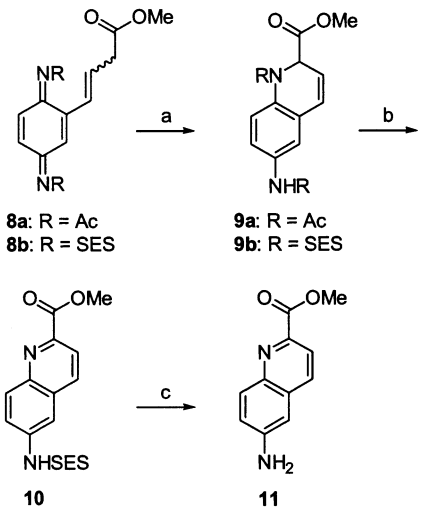
quinone di- and monoimides would then be accessible by oxidation.[8]

(6) Ortho quinone methide imines (from the thermolytic dehydration of *o*-(2-hydroxy-3-propenyl) anilines in refluxing xylene or *o*-dichlorobenzene for several hours) have been reported to undergo electrocyclization to 1,2-dihydroquinolines; see: Wiebe, J. M.; Caille, A. S.; Trimble, L.; Lau, C. K. *Tetrahedron* **1996**, *52*, 11705−11724.

(7) Stille coupling is reported not to proceed with free arylamines; see: Falcou, A.; Marsacq, D.; Hourquebie, P.; Duchêne, A. *Tetrahedron* **2000**, *56*, 225−231. Our own experience confirms this.

(8) The synthesis and physical and chemical properties of quinone di- and monoimides are described in the pioneering papers of Roger Adams. See, e.g.: Adams, R.; Reifschneider, W. *Bull. Soc. Chim. Fr.* **1958**, 23−65.

Scheme 3. Annulation of Diimide Substrates and Transformation of Dihydroquinolines to 6-Amino Quinolines[a]



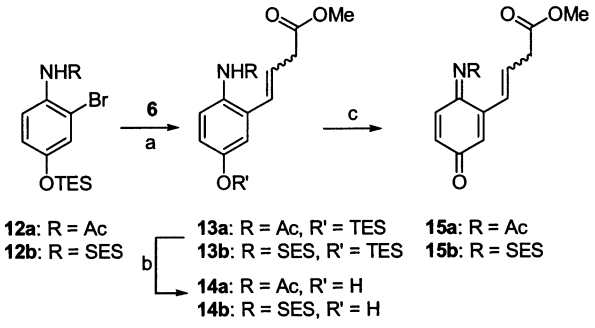
[a] (a) 5 mM in toluene, 5% HMPA, rt (55% **9a**, 60% **9b**); (b) for **9b**: TBAF or K_2CO_3, DMF, rt (quantitative); (c) 50% H_2SO_4, rt (80%).

The synthesis of quinone diimide substrates **8** was based on bromo phenylene diamine **4** (Scheme 2).[9] We prepared acetamide derivative **8a** by this three-step scheme. Acetylation followed by palladium-catalyzed coupling of substrate **5a** with vinyl stannane **6**[10] and finally oxidation of Stille product **7a** completed the synthesis of quinone diimide **8a**.

Addition of small amounts of HMPA[12] to a dilute solution of diimide **8a** at room temperature afforded the desired annulation product dihydroquinoline **9a** in good yields (Scheme 3). This conversion represents the first example of a new synthesis of protected dihydroquinolines.

Diacetamide **9a** was unreactive under standard deprotection conditions[13] and could not be carried forward efficiently. Therefore, with the goal of obtaining annulation products that could be deprotected under mild conditions, we tested the utility of the SES group[11] in the annulation scheme. Thus,

Scheme 4. Preparation of Monoimide Substrates[a]



[a] (a) **6**, $(Ph_3P)_4Pd$, toluene, reflux (76% **13a**, 50% **13b**); (b) 50% AcOH, THF (94% **14a**, 90% **14b**); (c) $Pb(OAc)_4$, $CHCl_3$ (quantitative for **15a** and **15b**).

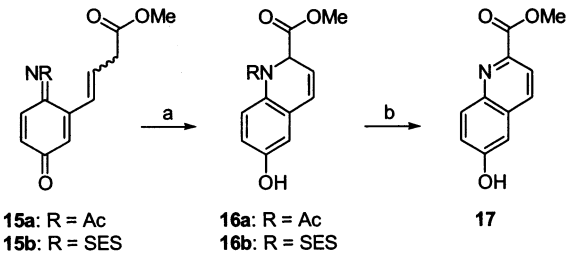
phenylene diamine **4** was converted to the di-SES derivative **5b** and the same coupling/oxidation sequence was applied, providing diimide substrate **8b**. Employment of the annulation conditions as described above cleanly provided dihydroquinoline **9b**. Treatment of the SES-protected dihydroquinoline **9b** with TBAF or with potassium carbonate resulted in aromatization with regiospecific loss of one of the two SES groups and quantitative formation of quinoline **10**. Liberation of the second amino group to afford *p*-amino quinoline **11** was achieved by stirring intermediate **10** in 50% sulfuric acid for 20 h.

Testing the scope of the new annulation methodology with vinyl quinone monoimide substrates was of particular interest because it would provide 6-hydroxy quinolines. 6-Oxygenated quinoline systems appear in the structures of a number of medicinally interesting and synthetically challenging natural products, including those of quinine, streptonigrin, and the luzopeptins.[14]

The synthesis of vinyl quinone monoimides is outlined in Scheme 4. The protected aminophenol **12a**[15] underwent Stille coupling with stannane **6**, and the resulting TES-ether **13a** was deprotected to give phenol **14a**. Oxidation afforded the desired annulation substrate **15a**.

As anticipated, addition of HMPA to a toluene solution of monoacetimide substrate **15a** at room temperature in the dark effected clean conversion to dihydroquinoline **16a**, successfully extending the methodology to 6-hydroxy quinoline systems (Scheme 5). However, attempts to remove the

Scheme 5. Annulation of Monoimide Substrates and Conversion of Dihydroquinolines to 6-Hydroxy Quinolines[a]



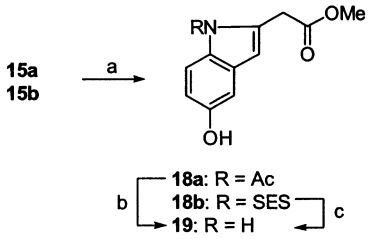
[a] (a) For **15a**: 5 mM in toluene, 5% HMPA, rt, dark (71%). For **15b**: 2 mM in toluene, 2.5% HMPA, reflux, dark (58%); (b) for **16b**: K_2CO_3, DMF, 50 °C or CsF, DMF, rt (quantitative).

acetyl group from this cyclization product, under conditions such as those applied to diacetamide **9a**, provided neither dihydroquinoline nor quinoline.[13]

Resorting again to the use of the SES protecting group, we prepared monoimide **15b** (Scheme 4) and subjected it to the cyclization conditions. This substrate proved to be stable at room temperature in the toluene/HMPA medium. However, when the solution was stirred at reflux in the dark, reaction was complete in 1 h and SES-protected dihydroquinoline **16b** was isolated in satisfying yields. Treatment of this compound with either base or a fluoride source effected both deprotection and aromatization, affording 6-hydroxyquinoline **17** in quantitative yields.

Remarkably, exposure of the same annulation reaction mixtures (monoimide **15a** or **15b** in toluene containing 0.5% HMPA)[16] to light at room temperature resulted in total conversion of the substrate to the protected indole (**18a** and **18b**) rather than to the protected dihydroquinoline system (Scheme 6).[17] Deprotection of each of these products

Scheme 6. Photochemical Reaction Conditions Yield Indole Products[a]



[a] (a) For **15a**: 5 mM in toluene, 0.5% HMPA, hν, rt (69%). For **15b**: 2 mM in toluene, 0.5% HMPA, hν, rt (59%); (b) NaOMe, MeOH, rt (quantitative); (c) CsF, DMF, rt (quantitative).

provided the corresponding 5-hydroxy indoleacetic acid ester **19**[18] in quantitative yield.

Although the photochemical isomerization of vinyl quinones to benzofurans is known,[19] the corresponding conversion of vinyl quinone imides to indoles is a new reaction. In the systems examined so far, the mild conditions required and the simplicity of the procedure were dazzling.

The synthesis of quinolines and indoles by a short sequence based on Stille coupling of protected bromo diamines and amino phenols followed by electrocyclization

(9) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797−11810.

(10) Collins, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G. *J. Med. Chem.* **1987**, *30*, 193−197.

(11) SES = trimethylsilylethanesulfonyl (Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099−2102).

(12) With the diimides, the rate of reaction accelerated with the amount of HMPA added up to approximately 5 vol %.

(13) Basic reaction conditions (NaOMe, MeOH) left dihydroquinoline **9a** unchanged, whereas acidic conditions (AcOH or up to 37% HCl) resulted in the formation of decomposition products.

(14) Total syntheses of each of these targets have been reported. For quinine, see: Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239−3242. For streptonigrin, see: Boger, D. L.; Panek, J. S.; Duff, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 5745−54. For luzopeptins, see: Boger, D. L.; Ledeboer, M. W.; Kume, M.; Searcey, M.; Jin, Q. *J. Am. Chm. Soc.* **1999**, *121*, 11375−11383. Valognes, D.; Belmont, P.; Xi, N.; Ciufolini, M. A. *Tetrahedron Lett.* **2001**, *42*, 1907−1909.

(15) For the preparation of protected amino phenols **12a** and **12b**, see Supporting Information.

(16) Employment of higher concentrations of HMPA resulted in the formation of mixtures of dihydroquinoline and indole products.

(17) The formation of indole products from diimide substrates **8a** and **8b** was not observed even after prolonged exposure to light or upon irradiation in a photochemical reactor in toluene containing HMPA.

(18) Related indoles have been used in nonpeptidic neurotensin mimetics; see: Dodd, D. S.; Kozikowski, A. P.; Cusack, B.; Richelson, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1241−1246.

(19) Iwamoto, H.; Takuwa, A.; Hamada, K.; Fujiwara, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 575−581.

of quinone imides provides the chemist with a new and attractive "disconnect" for retrosynthetic analysis. The mechanism of the photochemical indole synthesis and possible applications of the new methodologies for the preparation of nitrogen-containing heterocyclic natural products are currently under investigation.

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Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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